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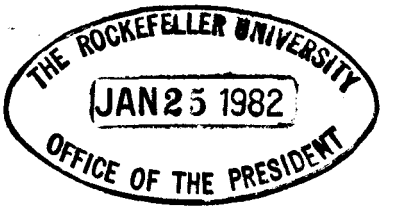

January 15, 1982

Dr. Joshua Lederberg
President
Rockefeller University
1230 York Avenue
New York, N. Y. 10021

Dear Dr. Lederberg:

Some time ago you asked Bob Mitchell for insight into how herbicide "safeners" work and how the people at Stauffer discovered the substituted dichloroacetamides which minimize the phytotoxic effects of thiocarbamate herbicides on the seed.

N,N-Diallyldichloroacetamide was the most effective of many N-substituted chloroamides and our friends at Stauffer tell us it resulted from study of hundreds of screening candidates.

The mechanism of action was reported by Lay, Hubbell and Casida[1,2] in 1975 and their description appears unchallenged since its publication.

Biological oxidation of the thiocarbamates to the corresponding sulfoxide probably constitutes the first step in corn phytotoxicity. Evidence in vitro indicates the sulfoxides carbamoylate glutathione and the safeners or antidotes act in corn to raise the glutathione and glutathione-S-transferase levels resulting in rapid detoxification of the sulfoxides.

I have seen no explanation why many substituted chloroacetamides are unique in increasing glutathione production.

Our research work at Virginia has focused on chemical synthesis to provide intermediates for the herbicide industry. With incorporation of Celanese's seed companies into Virginia's activities, we are

[1]Dichloroacetamide Antidotes for Thiocarbamate Herbicides: Mode of Action, Ming-Muh Lay, James P. Hubbell, John E. Casida, Science, 189, No. 4199, 1975, pp. 287-9

[2]Dichloroacetamide Antidotes Enhance Thiocarbamate Sulfoxide Detoxification by Elevating Corn Root Glutathione Content and Glutathione S-Transferase Activity, Ming-Muh Lay and John E. Casida, Pesticide Biochemistry and Physiology, 6, 442-456 (1976)

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expecting this emphasis to broaden and change as we try to match chemical R&D strengths to the production and marketing expertise of the seed companies. As yet, we haven't identified one single "silver bullet" to couple the agricultural and chemical expertise. We have enlisted our own and Corporate strength to identify appropriate strategies and we would be receptive to any comments you might have.

Very truly yours,

Matthew E. Hermes, Ph.D.
Director, Research & Development

MEH:esp
cc: R. L. Mitchell
L. C. Bostian
C. C. Braun